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10/565,507	10/02/2006	David Walterus Dekkers	DEKK3002/REF	9894

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BACON & THOMAS, PLLC
625 SLATERS LANE
FOURTH FLOOR
ALEXANDRIA, VA 22314-1176

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,507	DEKKERS ET AL.	
	Examiner	Art Unit	
	Alicia L. Fierro	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-13 and 15-17* is/are pending in the application.

4a) Of the above claim(s) *7-12 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,5,6,13,15 and 17* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/23/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. The instant application is a 35 USC 371 National Stage filing of international application No. PCT/GB04/003210, filed July 23, 2004, which claims priority from UK patent document 0317269.9, filed July 23, 2003.

Information Disclosure Statement

2. The information disclosure statement submitted on January 23, 2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed be submitted to the office. It has been placed in the application file, but the references which are crossed out in the signed copy of the 1449 form have not been considered because copies of the documents have not been received by the Office.

Election/Restrictions

3. Applicant's election with traverse of Group I (i.e. compounds of formula (I), claims 1-8, 13, 15 and 17) in the reply filed on October 22, 2009 is acknowledged. Further, Applicant's election of species in the same reply is acknowledged. The elected species is that of example 2, i.e. the di-glutathione substituted compound 4-OH-OPB-2GSH. The elected species is a compound of formula (IV) wherein R2 is butyl, R3 is H, R5 is H, each Y is S; each R6 is glutathione; and each Y-R6 group is ortho to the OH group. Claims 3-6, 13, 15 and 17 read on

the elected species. Claim 7 is not included because, since one Y group is required to be meta to the OH in the claim, it does not read on the elected species. Regarding claim 8, the claim is a product by process claim. The variable "X" is never defined in the instant claims so the instantly elected species is not interpreted as being produced by the process in claim 8. Applicant argues that the claims, as presently amended, contain a special technical feature which defines a contribution over the prior art. This argument is not found to be persuasive in view of the art applied under 35 U.S.C. 103 in paragraphs 16-19 below. Because obvious variants of the claimed compounds are known in the prior art (i.e. WO 01/00585 in view of US 2,674,600 for the reasons described in paragraphs 16-19 below), the technical feature shared by the claims is not a special technical feature.

4. The requirement is still deemed proper and is made FINAL.

5. The elected species was found to be free of the prior art. As such, the search was extended to include all compounds of formula (III) wherein R2 is butyl, R3 is H, R5 is H, and R6 is glutathione, cysteine, or alkyl.

Status of Claims

6. Currently, Claims 3-13 and 15-17 are pending in the instant application. Claims 7, 9-12 and 16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on October 22, 2009.

7. Claims 3-6, 13, 15 and 17 read on an elected invention and species and are therefore under consideration in the instant application.

Claim Objections

8. Claim 4 is objected to for being dependent on a rejected base claim, but would be allowable if rewritten in independent form including all limitations of the base claim and any intervening claims.

9. Claim 4 is objected to because the definition of R_6 (i.e. cysteine or glutathione attached via the sulphur atom) appears to be the definition of the group "Y-R_6" since both cysteine and glutathione already contain the necessary sulfur linking group. Appropriate correction or clarification is required.

10. Applicant is advised that should claim 3 be found allowable, claim 13 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, the intended use added in claim 13 does not add any limitations to the subject matter encompassed by claim 3.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 3, 5, 6, 13, 15 and 17 are rejected under 35 USC 112 1st paragraph as failing to comply with the written description requirement.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other

materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus …") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

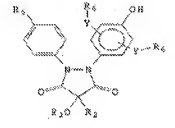
The MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The Guidelines for Examination of Patent Applications Under 35 USC 112, ¶1, "Written Description" Requirement (Federal Register, Vol. 66, No. 4, pg. 1105, column 3), in accordance with MPEP § 2163, specifically state that for each claim drawn to a genus the written description requirement may be satisfied through sufficient description of a representative number of species by a) actual reduction to practice; b) reduction to drawings or structural chemical formulas; c) disclosure of relevant, identifying characteristics (ie. structure) by functional characteristics coupled with a known or disclosed correlation between function and structure. The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention (Federal Register, Vol. 66, No. 4, p. 1105, 3rd column, 3rd paragraph). Below is such comparison.

It is noted that in the following the comparison is focused on products and not method of use. It is to be understood, however, that a *prima facie* conclusion of lack of written description for product implies the same conclusion for the process of use. In other words, the process of use cannot be practiced in absence of the product.

I. Scope of Claims

Compounds of the formula (III):



(III)

The following variables are claimed *broader* than what is supported by the disclosure (see below section II):

R_2 and R_6.

II. Scope of Disclosure

Reduction to Practice:

The compounds reduced to practice support the following definitions:

R_2: H or alkyl

R_6: cysteine or glutathione.

Reduction to Structural or Chemical Formulas:

The only disclosure, in addition to the species reduced to practice, is in form of a *list* of possible substituents for each variable. This type of disclosure is not viewed to be a representation of any of the species it entails. A "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus

because it would not "reasonably lead" those skilled in the art to any particular species. MPEP 2163.I.A. and *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996). Therefore, there is no disclosure of species (eg. by reduction to structural/chemical formulas) in addition to those reduced to practice.

Correlation between Structure and Function:

Furthermore, the instant specification does not disclose any specific correlation between function and structure. Thus, it is not understood what *specific structural elements* (pertaining to the specific claimed variables) are *essential* for the activity of the instantly claimed compounds.

III. Analysis of Fulfillment of Written Description Requirement:

In the absence of a correlation between structure and function of the specific variables in the instant claims, it is not possible to predict what modifications to the core structure will allow for the preservation of the desired activity.

In conclusion: (i) substantial structural variation exists in the genus/subgenus embraced by the rejected claims (ii) disclosure of species supporting genus is limited to compounds reduced to practice, which scope is not commensurate with the scope of genus/subgenus claimed; (iii) common structural attributes of the claimed genus/subgenus, combined with a correlation between structure and function, is neither disclosed in the instant application nor commonly known in the art. Thus, the specification fails to provide adequate written description for the genus of compounds claimed and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

13. Claims 3, 5, 6, 13, 15 and 17 are rejected under 35 U.S.C. 112, first paragraph because the specification does not reasonably provide enablement for making and using the extremely broad scope of compounds in claims 3, 5, 6, 13, 15 and 17 or for the broadly claimed intended

use in claim 13 "for use in therapy." The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. The nature of the invention
2. The state of the prior art
3. The predictability or lack thereof in the art
4. The amount of direction or guidance present
5. The presence or absence of working examples
6. The breadth of the claims
7. The quantity of experimentation needed, and
8. The level of skill in the art

(a) Wands analysis for scope of compounds

Particularly relevant to the instant case is the issue as to whether the specification provides embodiments allowing use of the claimed invention without requiring undue experimentation by one of ordinary skill in view of the highly unpredictable nature of affecting enzymes with chemical compounds.

> "[An inventor] must not be permitted to achieve . . . dominance by claims which are insufficiently supported and hence not in compliance with the first paragraph of 35 U.S.C. 112. That paragraph requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that,

> once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Accordingly, the critical element here how broad the claims are compared to the level of unpredictability in the art.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Breadth of the claims.

The scope of the invention is a genus of compounds having at least millions of species when the breadth of each variable is considered, particularly with R6 being any organic group having a molecular weight "up to around 500 amu" and R2 being any C1-C10 organic group. Without defining any particular structural features of these groups, the variables could potentially produce billions of combinations of different compounds.

Nature of Invention.

The nature of the invention involves pharmaceutical compounds for affecting enzymes and for pharmaceutical purposes.

State of the Art and Level of Skill in the Art.

The state of the prior art is that the drugs and the enzymes react in a lock and key mechanism and the structure of the compound has to be specific. Even a difference of a methyl group verses a hydrogen changes the properties altogether. A good example is a theophylline verses caffeine. They differ by just a methyl group but one of them has a pharmaceutical use as a bronchodilator. There is no absolute predictability and no established correlation between the different substitutions on a core that they would all behave pharmacologically in the exact same way. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

Although the level of skill in the art is very high, affecting enzymes is a very unpredictable art. Kubinyi (3D QSAR in Drug Design: Ligand-Protein Interactions and Molecular Similarity, Vol 2-3, Springer, 1998, 800 pages) teaches that very slight perturbations in the structure of an inhibitor (such as the addition of a methyl group or inversion of a chiral center, see p. 243) can have radical effects on the binding of the chemical compound.

Also the state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability and no established correlation between in vitro activity and the treatment of diseases as the in vitro data is not a reliable predictor of success even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

Number of Working Examples and Guidance Provided by Applicant.

The applicant provides experimental results of in vitro assays for only 1 of the instantly claimed compounds (particularly the instantly elected species of 4OH-OPB-2GSH). This one particular compound cannot possibly be considered representative of the very large genus claimed.

Because only one compound out of the billions of compounds of the claimed formula was tested in vitro, it is not possible to determine what amount of structural variation in these particular compounds allows for the retention of in vitro activity.

Unpredictability of the Art and Amount of Experimentation.

The art of using pharmaceuticals to affect enzymes is highly unpredictable as described by Kubinyi. In nearly every case, the skilled artisan could not predict *a priori* whether a given pharmaceutical would affect an enzyme. When small variations in structure such as the addition of a methyl group has radical effects on the binding of an inhibitor, without specific guidance or correlations indicating how the structure of species affects its ability to affect an enzyme, the scope of enablement is constrained to compounds showing substantial similarity to those actually demonstrated to be useful. Furthermore, there would be a huge amount of undue experimentation required in order to synthesize and screen the billions of compounds within the claimed scope.

Regarding how to make the instantly claimed invention, as stated in the preface to a recent treatise:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced

> for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) ....." Dorwald F. A. Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

Thus it is clear that it is not very easy to synthesize compounds. The various schemes in the specifications describe multistep reactions. In a multistep reaction, even when very similar starting materials are used, the products obtained are not necessarily similar. Due to the presence of large groups or functional groups which can interact with one another or even amongst themselves, completely different products could potentially be formed.
See pages 8 and 9 (of chapter 1 of Side reactions).

Considering the above factors, the claims are clearly not enabled for the full scope of the compounds claimed. The examiner recommends either amending the claim scope to only those compounds closely resembling the compounds actually tested and disclosed in the specification (specifically, the specification is enabling for the scope of the compounds of claim 4) or provide additional data and/or structural correlations to guide one of ordinary skill in the art to compounds possessing the asserted utility.

(b) Wands analysis for claimed intended use (claim 13)

The Nature of the Invention

Claim 13 is drawn to a compound of formula (III) for use in therapy. Due to the non-limiting claim language, the claims are interpreted to read on the compound having a therapeutic effect for the treatment of *any* disease or disorder.

The State of the Prior Art and the Predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases/conditions by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instantly claimed invention is highly unpredictable as discussed below: It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects, whether or not the diseases or conditions claimed are affected by the instantly claimed compounds and whether or not said compounds could possibly treat the myriad of diseases encompassed by the instant claims could take a lifetime of experimentation and clinical trials.

As one example, for the treatment of inflammatory diseases, these diseases are too divergent and can require different methods of treatment. Examples of disorders associated with inflammation include, but are not limited to: asthma, autoimmune diseases, chronic inflammation, chronic prostatitis, glomerulonephritis, hypersensitivities, inflammatory bowel diseases, pelvic inflammatory disease, reperfusion injury, rheumatoid arthritis, shoulder

tendonitis, transplant rejection, vasculitis, and various allergies. This broad list of diseases and conditions each has a different cause and, for the majority of the list, a different treatment. There is not one class of compounds, let alone one compound, which can treat all of these diseases or conditions.

For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process which can take place individually in any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reactions. There is no common mechanism by which all, or even most, inflammations arise. Accordingly, treatments for inflammation can normally be tailored to the particular type of inflammation present, as there is no, and there can be no, "magic bullet" against inflammation generally. Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilation and leaking of vessels. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. There are clusters of macrophages, which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters. This discussion demonstrates the extraordinary breadth and resulting unpredictability in the causes, mechanisms, and treatment (or

lack thereof) for inflammation. It establishes that it is not reasonable to accept any agent for the treatment of inflammation generally.

As a further example, for the treatment of viral or autoimmune disorders, these disorders are extremely broad but include or contemplate HIV, AIDS and Alzheimer's disease. Regarding Alzheimer's disease, the central characteristic of the disease is the deficiency in the level of the neurotransmitter acetylcholine, which is known to play an important role in memory functions. Alzheimer's disease is an extraordinarily difficult disease to treat and thus has been the subject of a vast amount of research. Despite an enormous number of different approaches, the skill level in the art is so low relative to the difficulty of the task at hand, that the only success has come from the treatment by compounds which are acetylcholinesterase inhibitors (Aricept®, Cognex®, Exelon® and Reminyl®), a property which the claimed compounds are not disclosed or known in the art to have.

The examples provided above are certainly not exhaustive, as it would be impossible to describe the skill level and unpredictability for each of the millions of diseases encompassed by the instant claim, it is clear from the above analyses that there is a great degree of unpredictability in the art area.

The Amount of Direction / Guidance Present and the Presence or Absence of Working Examples

The specification includes no working examples to demonstrate the treatment of any and all disorders, including inflammatory, viral and autoimmune disorders. The only direction or guidance present in the instant specification is the description of an in vitro assay that could be carried out to determine the effect of the compounds on inhibition of cytokine inhibition. In this

assay, only one compound (namely the instantly elected species) was tested and shown to be effective for this purpose. The determination that one compound, out of a claimed genus reasonably including at least billions of compounds, is effective at inhibiting cytokine production in vitro, cannot be said to reasonably correlate to the treatment of the diseases encompassed by the instant claim, which includes but is not limited to all viral, autoimmune, neoplastic, inflammatory and allergic conditions. As such, the specification appears to support the use of the compounds of claim 4 for the *in vitro* inhibition of cytokine production, but not for the use of any of the claimed compound for therapy as claimed. Also, the in vitro assay data as a whole does not describe all the types of inflammation, viral, or autoimmune disorders that can exist, or from which disease(s) they may stem. Thus, the specification does not contain any evidentiary support that the claimed compounds would be able to treat any of the claimed diseases.

The breadth of the claims

The scope of the claims involves billions of compounds of claim 3 as well as millions of diseases embraced by the claimed "use in therapy." One compound could not possibly be effective for the treatment of the entire instantly claimed genus of diseases and conditions, as evidenced by the unpredictability in the art area.

The level of the skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art as described above, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine whether the compound exhibits the desired pharmacological activity and which specific disease conditions would benefit from this activity. The amount of guidance or direction

needed to enable the invention is inversely related to the degree of predictability in the art. *In re Fisher*, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. *In re Fisher*, 427 F.2d 839, 166 USPQ 24; *Ex Parte Hitzeman*, 9 USPQ 2d 1823.

Thus, the specification fails to provide sufficient support for the broadly claimed compounds and their intended use recited in the instant claim, as a result necessitating one of skill to perform an exhaustive search for which diseases and conditions can be treated by any of the claimed compounds in order to practice the claimed invention.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which disease out of the millions encompassed by the claims would be treated by a reasonable number of the claimed compounds and which specific compounds would do so.

No compound has ever been found to treat diseases of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of modern medicine.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instantly claimed

methods. In view of the breadth of the claim, the chemical nature of the invention, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated or prevented by the compound encompassed in the instant claims, with no assurance of success.

Claim Rejections – 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. Claims 3, 5, 6, 13, 15 and 17 are rejected under 35 U.S.C. 103(a) as obvious over Tjotta et al. in WO 01/00585, published January 4, 2001, in view of Haefligher, U.S. Patent No. 2,674,600.

17. The '585 publication teaches compounds which are very structurally similar to those in the instant claims, as well as pharmaceutical compositions of said compounds. It states that the compounds have anti-inflammatory activity (see, e.g., p.1, paragraph 1). Specifically, the compound 4OH-OPB is described as being a preferred compound in the reference and is the only compound of the reference to be tested in any assay (see Example 18). Because this compound is described as being preferred, there would be motivation to select it for further modification to create further compounds also useful as anti-inflammatory agents

18. The difference between 4OH-OPB and the instantly claimed compounds is the presence of at least one Y-R6 group on the phenyl ring.

19. Haefliger teaches derivatives of 3,5-dioxo-pyrazolidine as anti-inflammatory compounds (see column 1, line 53). Specifically, the compound 1,2-di-(o-methyl mercapto phenyl)-3,5-dioxo-4-n-butyl-pyrazolidine is taught (see column 1, line 5 and claim 1). This compound contains a phenyl substitution identical to the instantly claimed compounds where one Y group is S and R6 is methyl, and the other Y is H, but differs from the instant compounds in that the 4-hydroxy substituent on the phenyl ring is not present.

20. It would have been *prima* facie obvious for one of ordinary skill in the art at the time the invention was made to combine the two compounds known in the prior art (namely, 4OH-OPB '585 publication and the generic structure of the SCH3 taught by Haefliger) which are taught to be useful for the same purpose (i.e. anti-inflammatory compounds). "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ....[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). One skilled in the art would expect success because upon the addition of the SCH3 to the phenyl ring, since compounds with this identical substitution are taught by Haefliger to also be useful as anti-inflammatory compounds. Thus, the skilled artisan would reasonably expect success in this combination.

Conclusion

21. No claims are allowed.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alicia L. Fierro whose telephone number is (571)270-7683. The examiner can normally be reached on Monday - Thursday 6:00-4:30 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alicia L. Fierro/
Examiner, Art Unit 1626

/Golam M. M. Shameem/

Primary Examiner, Art Unit 1626